UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,207	09/09/2003	Steven E. Cwirla	44368-0003 US C1	4104

25213 7590 11/29/2007

HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
XIE, XIAOZHEN	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
11/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,207	CWIRLA ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *162-178* is/are pending in the application.

4a) Of the above claim(s) *171-174* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *162-170 and 175-178* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070607*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Information Disclosure Statement (IDS) filed 7 June 2007 has been entered. Applicant's amendments of the specification filed on 1 September 2004, and 26 September 2006 have been entered. Applicant's amendment of the claims filed 30 August 2007 have been entered.

Election/Restrictions

An original Requirement for Restricition Election was mailed on 20 April 2006. In responses received on 26 September 2006 and 12 February 2007, Applicant elected Group I, claims 162-170, and elected species of SEQ ID NO: 209 for a peptide chain, and one compound with the structure of claim 165 wherein each moeity is identified. Upon further review, it appears that the generic claims (claims 162 and 165) can not be allowed unless all species (millions of species) are examined. In a telephonic interview with Attorney Jeffery Bernhardt in the presence of Examiner's supervisor, Gary Nickol, it was agreed that a revised Requirement for Restricition Election will be sent to Applicant which will limit the number of species examined (a total of six SEQ ID NOs and six compounds with each moiety identified). A revised Requirement for Restricition Election was mailed on 8 August 2007.

In a response received on 30 August 2007, Applicant elected **Group I, claims 162-170**, and species for a total of six SEQ IDs (**SEQ ID NO: 209, 210, 211, 212, 213 and 343**). Applicant further elected each moiety for the compound of claim 165 as:

R^1 and R^2: above SEQ IDs

n1: zero

n2: zero

n3: zero

n4: zero

x: one (1)

y: zero

Lk: lysine amide

In a telephonic interview with attorney Jeffery Bernhardt on 1 November 2007, it was further confirmed that the moieties for R^1 and R^2 are identical, i.e., R^1 and R^2 have the same SEQ ID.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-161 are cancelled. Claims 175-178 have been added. Claims 162-178 are pending. Claims 171-174 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 162-170 and 175-178 are under examination.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states,

"the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

Claims 167 and 170 are objected to because of the following informalities:

In claim 167, "claims 162" should be "claim 162". In claim 170, the word "any" should be deleted from the phrase "the compound of any claim 162". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 162-170 and 175-178 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a compound, a pharmaceutical composition thereof, comprising a peptide chain approximately 17 to 40 amino acids in length that binds to G-CSF and contains a sequence of amino acids selected from the group consisting of SEQ ID NOs: 209-213 and 343; wherein the compound contains a disulfide bond; and

wherein the N-terminus of the peptide is coupled to a polyethylene glycol molecule or is acetylated, and the C-terminus is amidated; wherein the compound comprising a peptide chain dimer having a generic structure as illustrated in claim 165.

The claims are broad in that they encompass a genus of molecules. What applicant has described in the specification are synthetic peptides having the amino acid sequence as indicated in Table 1 (pp. 45), and peptide dimers, modified peptides or dimers (e.g., PEGylated, acetylated, and/or amidated at the N- or C-terminus), and some of these peptides or mimetics can form disulfide bond between two peptide chains (Table 2, pp. 48-50). Applicant has described that some of these peptides or peptide mimetics exhibit binding specificity to G-CSF receptor and competing with G-CSF for binding to its receptor (see results in Table 1 and 2). Applicant, however, has not described the genus of the G-CSFR binding peptides, e.g., a peptide chain approximately 17 to 40 amino acids in length and contains a sequence of amino acids shown in SEQ ID NOs: 209-213 and 343, nor for the genus of molecules having a dimeric structure shown in claim 165, that exhibit G-CSF binding and antagonizing activities. While the claims recite the specific amino acid sequences that are contained in the peptide chains, e.g., SEQ IDs recited in the claims, Applicant has not provided sufficient teachings as to what additional amino acid residues are included in the peptide chain, and how long these molecules are. There is no teaching regarding the relationship of structure to function, such as what structural features are required for these molecules to possess the recited properties (e.g., G-CSF binding). Thus, the claims encompass a genus of molecules, which vary substantially in composition, and

could have very different structural and functional characteristics from the polypeptides that Applicant has disclosed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making of the claimed product, or any combination thereof. In this case, there is no identification of what additional amino acids can be added so that the molecule exhibits the recited properties. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of peptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound

itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only compounds comprising peptides or peptide mimetics that exhibit G-CSF binding and competing activities as shown in Table 1 and Table 2, including peptides of SEQ ID NOs: 209-213 and 343, and dimers thereof, but not the full scope of the claimed compounds are adequately described in the disclosure.

Claims 162-170 and 175-178 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a compound that binds to G-CSF, a pharmaceutical composition thereof, wherein the compound comprises a peptide chain selected from the group consisting of SEQ ID NO: 209, 210, 211, 212, 213 and 343; and wherein the compound comprises a peptide chain dimer having the structure as shown in claim 165, in which* R^1 *and* R^2 *are identical and selected from the group consisting of SEQ ID NO: 209, 210, 211, 212, 213 and 343, n1-4 and y are zero, x is one, and Lk is lysine amide;* does not reasonably provide enablement for any compound, including those comprising a peptide chain of approximately 17 to 40 amino acids in length, and contains a sequence of the recited SEQ IDs, nor for any dimerized peptide chain compounds. The specification does not enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

As set forth above, the specification discloses synthetic peptides having the amino acid sequences as indicated in Table 1 (pp. 45), and peptide dimers, modified peptides or dimers (e.g., PEGylated, acetylated, and/or amidated at the N- or C-terminus), and some of these peptides or mimetics can form disulfide bond between two peptide chain(s) (Table 2, pp. 48-50). The specification discloses that some of these peptides or peptide mimetics exhibit binding specificity to G-CSF receptor and competing with G-CSF for binding to its receptor (see results in Table 1 and 2), and these peptides include those set forth in SEQ ID NOs: 209-213 and 343. The specification, however, does not provide supporting evidence for the genus of

compounds exhibiting the same binding activity to G-CSF, e.g., a peptide chain approximately 17 to 40 amino acids in length and contains a sequence of amino acids shown in SEQ ID NOs: 209-213 or 343, nor for the dimerized peptide chain thereof. While several hundred peptide sequences are disclosed in the specification, only limited number of peptide chains and their dimers are tested for G-CSF binding (see Examples, and results in Table 1 and 2). Because these peptides vary in composition and structure, the few tested compounds are not sufficient to provide support for the whole genus. The art teaches that even minor changes in sequence can result in major changes in function, especially if the minor sequence change occurs within an active site or alters the overall conformation of the protein molecule. For example, Kirsch et al. (EMBO J., 2000, 19(13):3314-3324) showed that single amino acid mutations introduced into a BMP-2 protein could alter its biological activity from superagonistic (e.g., variant D53A and variant E109R) to antagonistic (e.g., variant A34D and variant L90A) (pp. 3317, Fig. 2). Since the specification does not define what structural characteristics these molecules have, one of skill in the art would evaluate all non-exemplified peptide chains and their dimers for binding and antagonizing activities towards G-CSF protein. Thus, undue experimentation would be required for the artisan to make and use the invention as broadly claimed.

Due to the large quantity of experimentation necessary to generate the nearly infinite number of peptide chain-containing compounds and their dimers recited in the claims, and screen same for G-CSF binding and agonizing/antagonizing activities and determine if these molecules can provide pharmaceutical uses, the lack of

direction/guidance presented in the specification regarding which structural features are required in order to provide activities and therapeutic effects, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fails to recite the structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
November 16, 2007

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER